REMARKS/ARGUMENTS

Reconsideration and allowance of the present application based on the following remarks are respectfully requested.

Upon entry of this Amendment, claims 1, 2, and 4-26, as amended, will be pending, of which claims 1, 14 and 22 are independent; claims 14-25 are withdrawn from consideration. None of the claim amendments introduce new matter into the application.

At the outset, however, Applicants, acknowledge with appreciation the courtesy and cooperation by the Examiner and her supervisor during a recent interview wherein the Section 112, first paragraph issues were discussed, as set forth in the Examiner Interview Summary. Applicants also acknowledge with appreciation that the pending claims are considered to be free of the prior art. Accordingly, the claims have again been amended to avoid the assertions of indefiniteness; to remove claim objections; and to address the issues of enablement and written description along the lines discussed during the aforementioned interview.

The various parts of the **DETAILED ACTION** will now be addressed.

The specification is objected to for not complying with the sequence rules in that the previously submitted sequence listing was found to contain error(s) as shown in the attached raw sequence listing error report. Accordingly, a corrected Sequence listing together with a computer-readable form of same are provided herewith. Also enclosed is a Statement to Support Filing and Submission in Accordance with 37 C.F.R. §§ 1.821-1.825. No new matter is added.

Reconsideration of the restriction requirement and rejoinder of claims 14-25 is respectfully requested. Appropriate claim amendments to conform to the current amendments will be presented should rejoinder occur. It is appreciated that previously added claim 26 is deemed to be drawn to the elected invention and is examined herein.

Information Disclosure Statement

The entry of the Statement submitted on January 9, 2004 is appreciated. As informed in the Examiner Interview Summary, the next communication from the Patent and Trademark Office will acknowledge, by return of an initialed and dated copy, the Information Disclosure Statement and Form PTO 1449, filed January 23, 2002.

Claim Objections

2. The objection to claims 1 and 26 are obviated by the current claim amendments.

3. The objection to claims 2-13 is obviated by the current amendments replacing "Method" with "The method."

4. The current amendment to claim 7 addresses the objection to this claim. A similar amendment is made in claim 8.

5. Claim 7 is amended to replace the term "switched on" (twice) with the more commonly used term "induced." The term "switched on" does not appear in claim 6. Accordingly, the objection to claims 6 and 7 is avoided and/or traversed.

Claim Rejections - 35 U.S.C. § 112, Second Paragraph

7. Claims 1-2, 5-13 and 26 are considered indefinite because the presence of the thioesterase releasing factor is not positively recited and, therefore, an "essential step" is considered to be missing. Although Applicants do not agree, nevertheless, to expedite prosecution and allowance, the feature of claim 3 is incorporated into each of independent claims 1 and 26. Accordingly, this basis for rejection should be withdrawn.

8. Claim 2 is considered to be indefinite in the recitation of "wherein the condensation domain ... is covalently bound to the module recognizing ... ." This recitation is considered to be confusing in light of the earlier recitation "comprising two minimal modules connected by one condensation domain." (Emphasis by Examiner.) The Examiner states that "connected" implies a physical linkage, such as a covalent bond. To avoid confusion, the Examiner has proposed that claims 1 and 26 be amended to recite, "comprising two modules, a condensation domain and a thioesterase domain."

In the present application the term "connected" is defined on page 11, lines 30-32, as meaning that the "condensation domain ensures that both minimal modules can operate concertedly." Furthermore, it is explained on page 11, lines 20-30 that the "condensation domain ... does not need to be bound covalently to both minimal modules ... because there is no requirement that these two minimal modules are located on a single polypeptide chain.

Thus, the expression "covalently bound to the module recognizing L-aspartic acid" further limits claim 1 since in claim 1 only the second minimal module (recognizing L-Phe) is required to be covalently bound. In claim 1, the minimal domain recognizing L-Asp does not need to be covalently bound to the condensation domain. Thus, claim 2, which is directed to

this embodiment of the invention, does further limit claim 1. In this regard, the term "connected" as used in the claims does not render the claims to be indefinite.

Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

Claim Rejections - 35 U.S.C. § 112, First Paragraph

10/11/12. Claims 1-13 were again rejected as failing to comply with the written description requirement. Applicants respectfully disagree and traverse this rejection for at least the following reasons.

During the recent interview, Applicant's representative presented alignment charts for adenylation domains for a series of Asp and Phe A-domains. These alignment charts illustrated that the core motifs A-1 through A-10, as shown in the Table on page 9 of the specification (which table was based on the data in the printed publication Marahiel et al, of record) are substantially present in each of the A-domain sequences. A copy of the alignment charts: "Asp activating A-domains," "Phe activating A-domains," and "alignment Asp and Phe activating A-domains" which were presented at the interview are attached hereto. Also enclosed for further understanding of the relationship of the A-domains from a representative range of non-ribosomal peptide synthetases is a "pair distance" table, "Pair Distances of Asp/Phe A-domains Clustal W(Slow/Accurate, Gonnet[1]) which includes data for the percent similarities among and between the A-domains for Asp, the A-domains for Phe and among and between the A-domains for Asp and Phe.

The presentation of the alignment data was found persuasive of the enablement and written description so long as the claims were modified to include some structural features which bear a correlation with known adenylation domains (A-domains).

Therefore, as now more clearly recited in the pending claims, the adenylation domain of each minimal module is "identifiable by having at least substantial structural homology with the core motifs [A-1 through A-10] having SEQ ID NOs: 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 found in naturally occurring non-ribosomal peptide synthetases." That is, as demonstrated by the alignments of representative known non-ribosomal peptide synthetases, the sequences of the core motifs, while not identically present (other than for A-5, SEQ ID NO:5), are substantially present in substantially all peptide synthetases.

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[1] Thompson, JD; Higgins, DG; Gibson, TJ (1994): CLUSTAL W: improving the sensitivity of progressive multiple sequence alignment through sequence weighting, position-specific gap penalties and weight matrix choice" Nucleic Acid Res., 22(22):4673-80.

For example, for the core motif A-1 (SEQ ID NO:1), having the general sequence L(TS)YxEL, the corresponding sequence for the A-1 core motif of TYC-B3A is: MSFREL; namely, M in place of L at the first position, and F in place of Y at the third position, both generally conservative substitutions. For the A-2 core motif, TYC-B3A has the sequence: LKAGGAFLPVD whereas A-2 (SEQ ID NO:2) has the sequence: LKAGxAYL(VL)P(LI)D, again only minor differences.

Similarly, at least substantial homologies with the remaining core motifs A-3 through A-10 are present for each of the aligned sequences. Furthermore, it is appreciated that these sequences are representative of the sequences for the A-domains which have specificities for amino acids other than Asp and Phe. This is true, not only for these representative non-ribosomal peptide synthetases, but also for non-ribosomal peptide synthetases which are not included in these charts. By virtue of these at least substantial homologies, the core motifs make it possible to identify the A-domain of any particular non-ribosomal peptide synthetase. That is, it is understood that "substantial structural homology" would be understood by those skilled in the art and having in mind the specification of this application and the knowledge of the variations in even the highly homologous core motifs, that variations in some or all of the sequences of the core motifs is within the scope of the invention consistent with the variations found in the naturally occurring sequences of A-domains of non-ribosomal peptide synthetases, yet which are still sufficient to identify a sequence as an A-domain.

Moreover, at the interview, it was also explained, as described in the specification and the literature, that in view of the co-linearity of peptide synthetases it is relatively routine to identify the A-domains for each particular amino acid once the sequence of the polypeptide produced by a particular non-ribosomal peptide synthetase is known. Therefore, by combining the knowledge of the core motifs with the co-linearity of non-ribosomal peptide synthetases, and the knowledge of the general construction of the minimal modules of these peptide synthetases, those skilled in the art would recognize that Applicants were in possession of the subject matter being claimed. Furthermore, given this knowledge and following the guidelines of the examples in the specification as well as demonstrated in the literature, such as the references to Marahiel et al, Chem. Rev. 1997, 97, 2651-2673; and Stachelhaus et al, Chemistry & Biology, Research Paper, 1999, 6(8): 493-505; and the other references of record, it would not require undue experimentation to identify A-domains that recognize Asp and Phe and to construct the two minimal modules as set forth in the pending claims over the entire scope thereof.

The specification does, by specific example, and by general descriptions (*see, e.g.,* pages 4- 6) set forth the functional and structural properties of non-ribosomal peptide synthetases which are applicable to non-ribosomal dipeptide synthetases. One skilled in the art would have no difficulty in ascertaining whether any particular structure functions as non-ribosomal dipeptide synthetase. The specification provides detailed descriptions of the minimal modules which exist at clearly defined positions within the context of the larger non-ribosomal peptide synthetases. These have very characteristic structures, also at the level of the amino acid sequence of the protein produced.

Under these circumstances, and taking into consideration that the present Applicants were the first to discover and report that the dipeptide Asp-Phe could be produced using non-ribosomal dipeptide synthetases, the specification does include enough detail for one of ordinary skill in the art to understand what is claimed and to recognize that the inventor invented what is claimed.

Accordingly, reconsideration and withdrawal of the rejection of claims 1-13, under the first paragraph of 35 U.S.C. 112, for lack of written description, is respectfully requested.

13/14/15. For substantially the same reasons why the specification satisfies the written description requirement, the specification also satisfies the enablement requirement. Again, the rejection does not assert that there is not enablement for at least the exemplified embodiments. However, it was asserted that undue experimentation would be required to practice the entire scope of the claimed invention.

Applicants respectfully disagree.

As stated above, the currently amended and pending claims recite sufficient structural details of the minimal modules for recognizing Asp and Phe, combining these amino acids, and releasing Asp-Phe, so that the practitioner of ordinary skill would be enabled to make and use the claimed invention correlated to the entire scope of what is being claimed.

Accordingly, reconsideration and withdrawal of the non-enablement rejection is respectfully requested.

Therefore, all objections and rejections having been addressed, it is respectfully submitted that the present application is in a condition for allowance and a Notice to that effect is earnestly solicited.

Should any issues remain unresolved, the Examiner is encouraged to contact the undersigned attorney for Applicants at the telephone number indicated below in order to expeditiously resolve any remaining issues.

Respectfully submitted,

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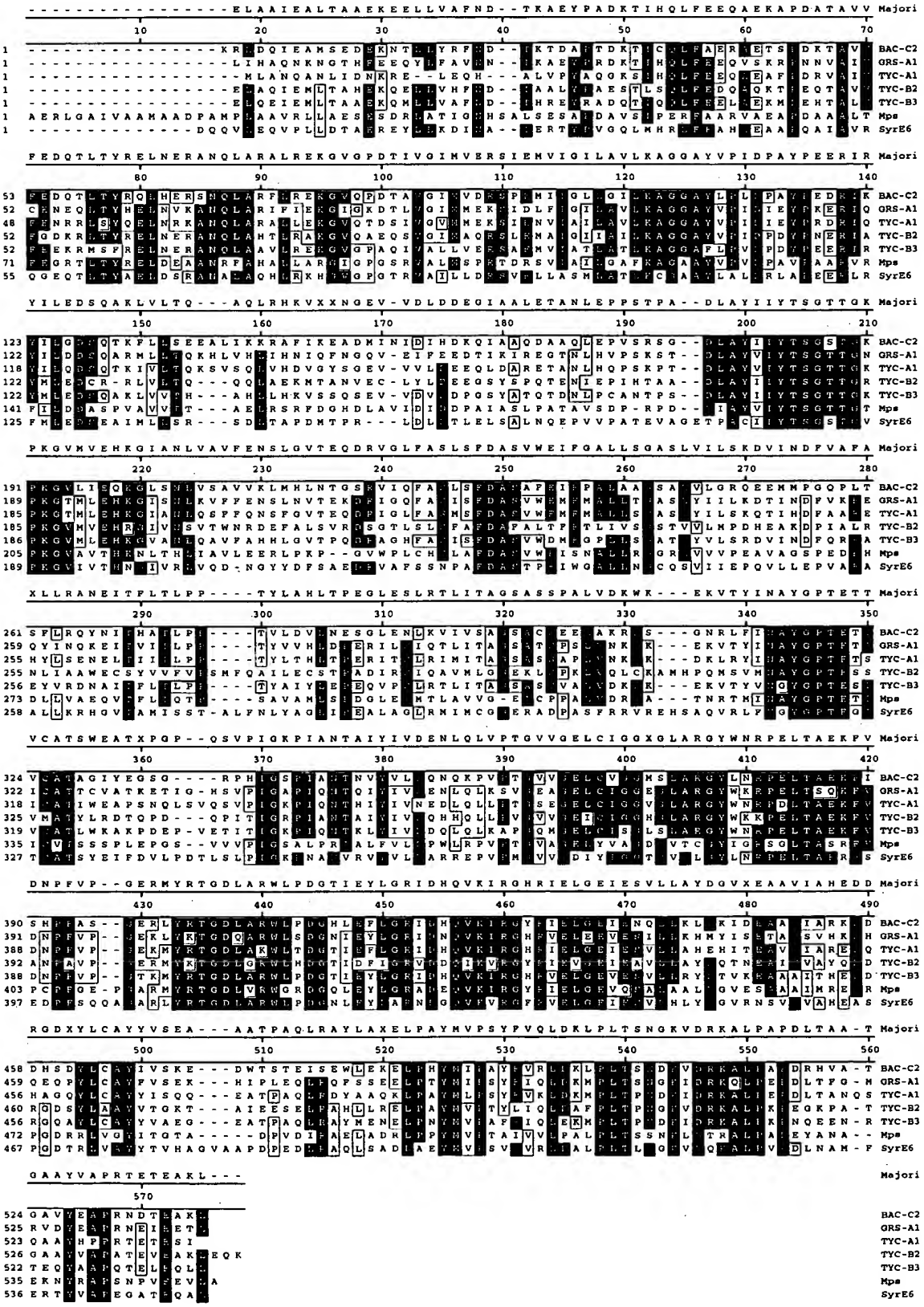
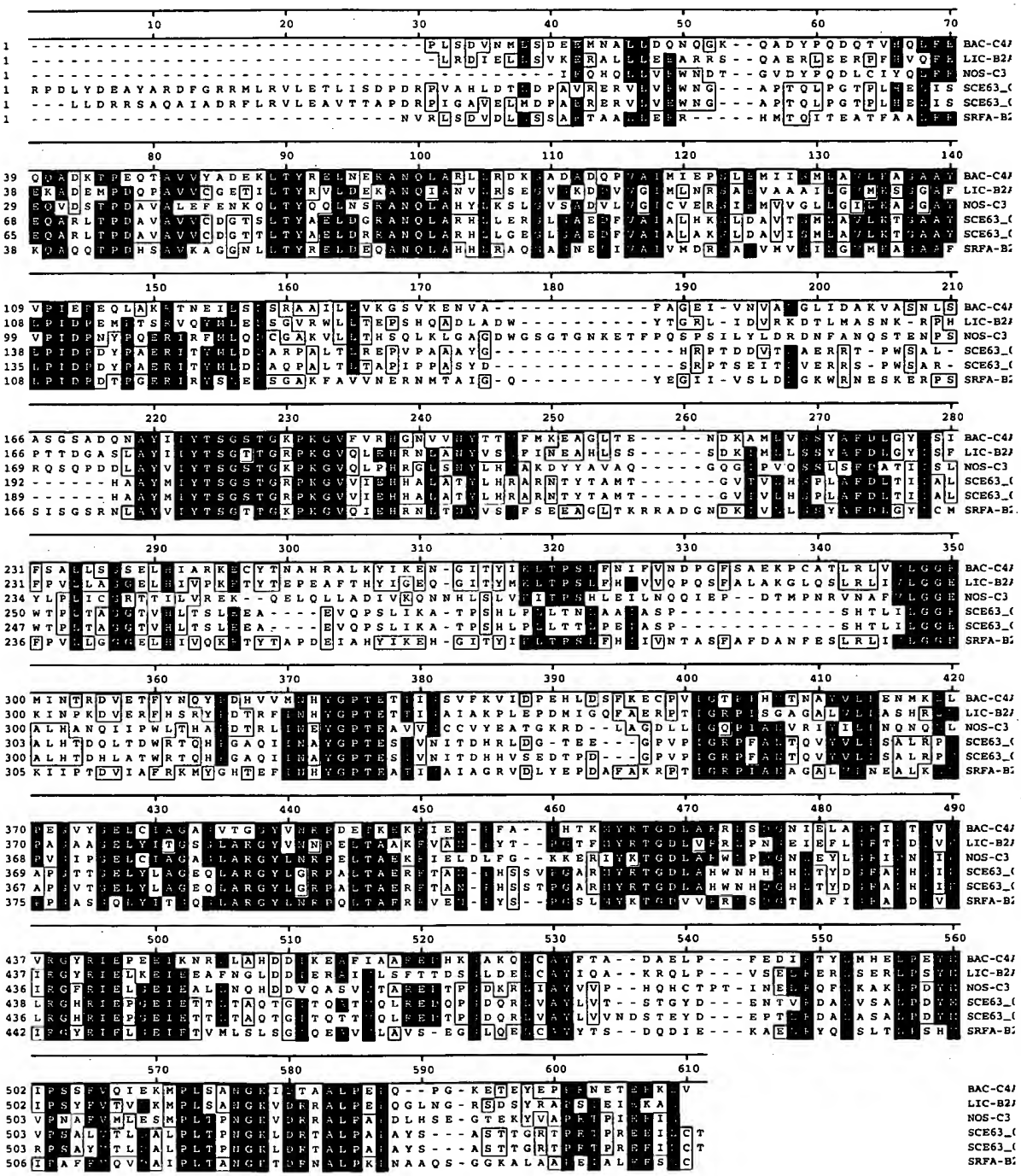
Date: August 5, 2004
Attachments: Sequence Listing (paper copy and diskette) with Statement to Support Filing
Alignment charts (3) and Pair Distance Chart

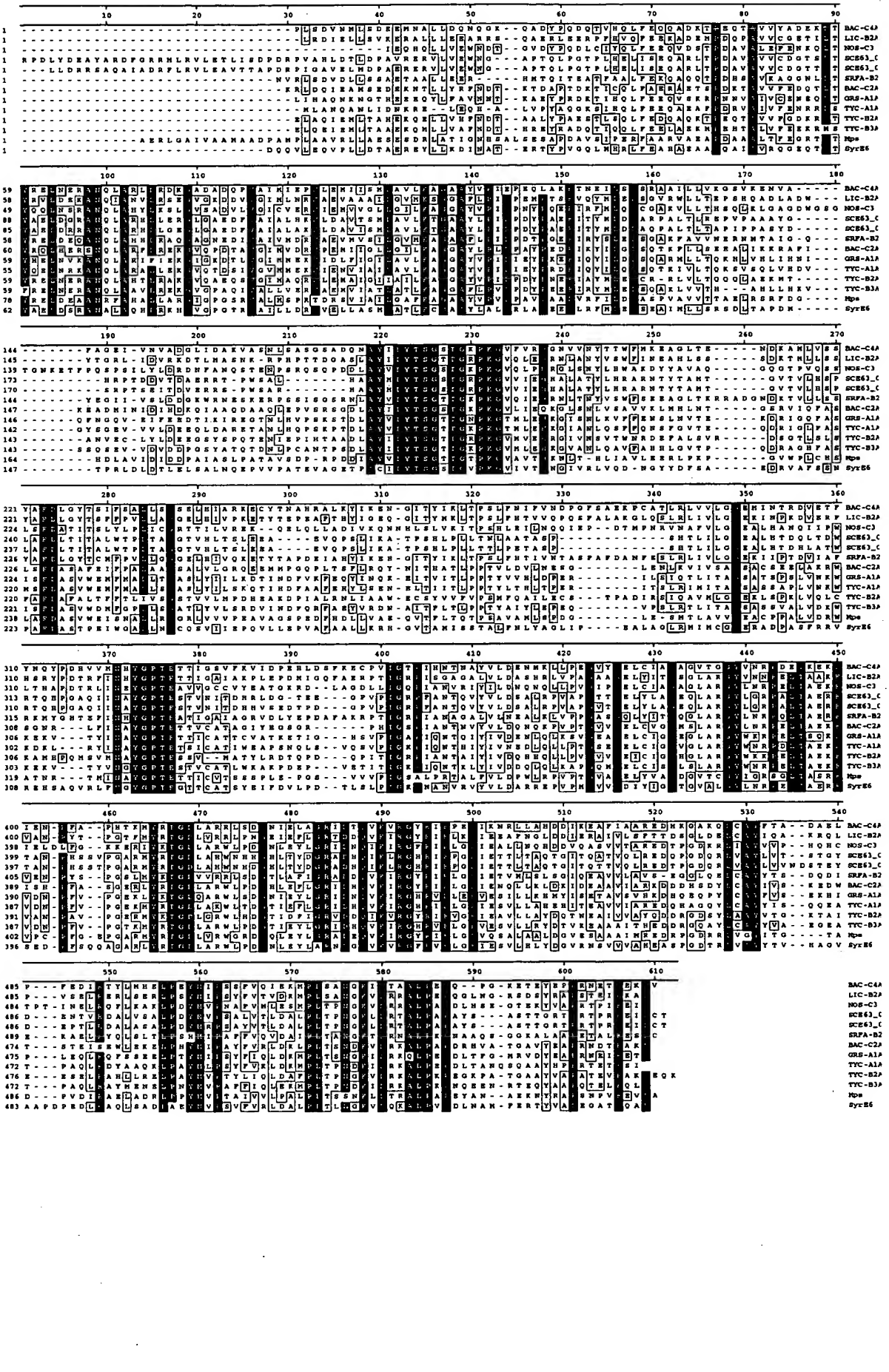
Phe activating A-domains



Asp activating A-domains



alignment Asp and Phe activating A-domains



Pair Distances of Asp/Phe A-domains ClustalW (Slow/Accurate, Gonnet)

Percent Similarity

	BAC-C4A	**LIC-B2A**	**NOS-C3**	**SCE63_02c**	**SCE63_03c**	**SRFA-B2A**	BAC-C2A	GRS-A1A	Mps	SyrE6	TYC-A1A	TYC-B2A	TYC-B3A
BAC-C4A	***	46.9	37.6	35.8	35.0	45.6	**41.4**	**40.3**	**32.5**	**34.9**	**41.8**	**40.5**	**40.7**
LIC-B2A		***	37.9	33.3	33.3	55.4	**40.9**	**37.8**	**34.8**	**36.1**	**37.9**	**41.4**	**38.6**
NOS-C3			***	40.0	40.2	35.8	**42.6**	**40.8**	**32.4**	**38.7**	**41.4**	**42.4**	**41.6**
SCE63_02c				***	87.3	36.9	**34.9**	**31.2**	**37.5**	**34.7**	**35.6**	**36.1**	**33.4**
SCE63_03c					***	38.0	**35.9**	**32.5**	**38.4**	**36.0**	**36.2**	**36.6**	**34.7**
SRFA-B2A						***	**39.4**	**35.4**	**32.0**	**36.5**	**38.6**	**41.1**	**39.9**
BAC-C2A							***	44.8	39.8	38.5	45.9	43.7	47.0
GRS-A1A								***	34.0	34.9	60.6	41.4	53.4
Mps									***	35.5	34.5	30.0	37.5
SyrE6										***	34.3	36.5	38.6
TYC-A1A											***	41.6	56.2
TYC-B2A												***	47.9
TYC-B3A													***

BAC – Bacitracin *Bacillus licheniformis*; GRS – Gramicidin S *Bacillus brevis*; LIC – Lichenysin *Bacillus licheniformis*; NOS – Nostocpeptolide *Nostoc sp.* GSV224; SCE63 – CDA *Streptomyces coelicolor*; SRF – Surfactin *Bacillus subtilis*; Syr – Syringomycin *Pseudomonas syringae*; TYC – Tyrocidine *Bacillus brevis*

domain names in bold: Asp activating A-domains
domain names underlined: Phe activating A-domains

percent values in bold: comparison Asp- with Phe-A-domains